Case SH2017-0039

MDS arising in a 13-year-old with *RUNX1* familial platelet disorder

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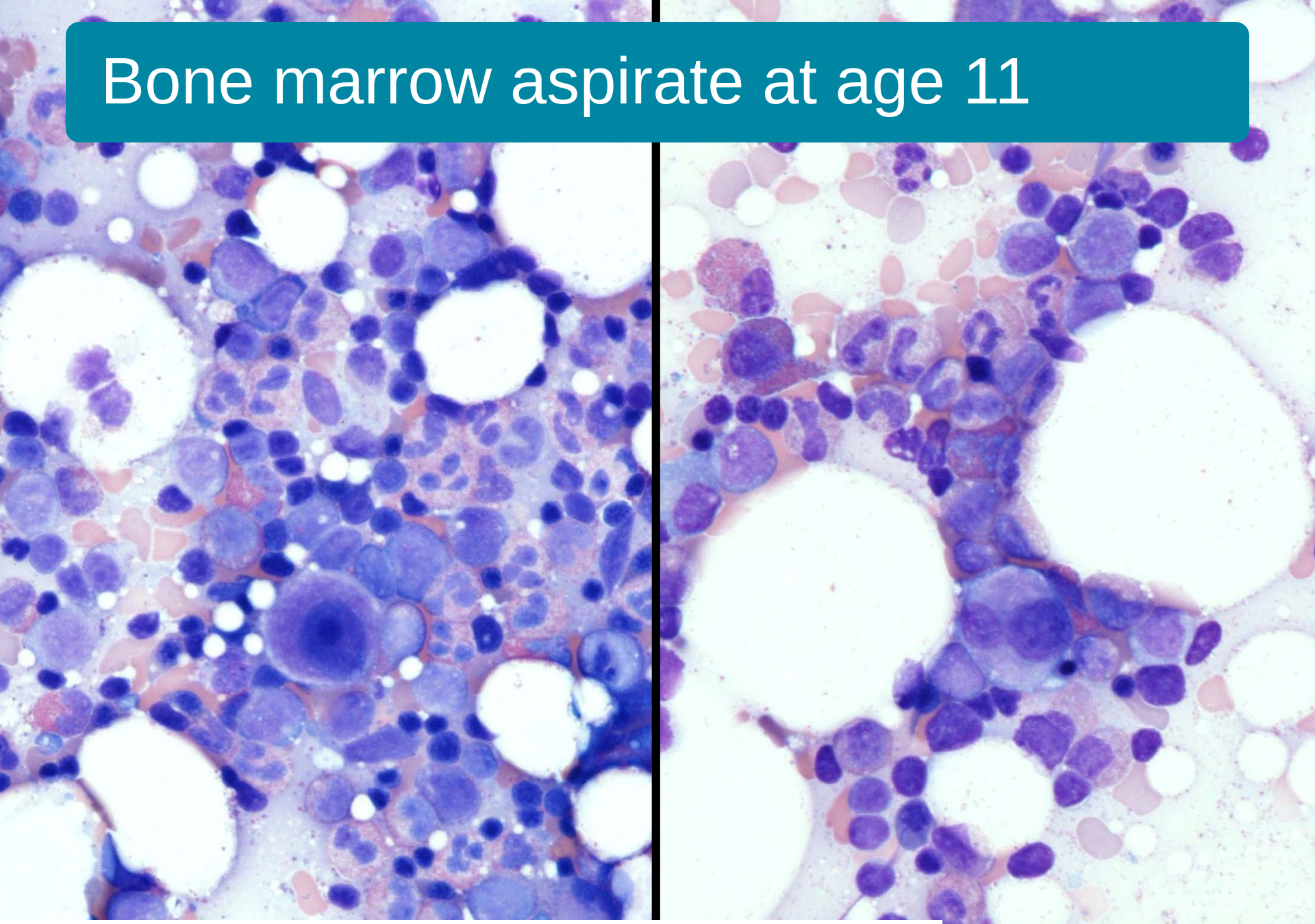
Clinical History

- 13 year old boy
  - Age 11
    - Thrombocytopenia (68 K/μL) in the setting of a chronic idiopathic elevation of CK and myopathy of unclear etiology
    - CBC also showed neutropenia without anemia
  - Thrombocytopenia could be tracked back to the newborn period (29-90 K/μL)
  - No history of excessive bleeding
  - Adopted at 4 months of age (no available family history)

Clinical History, continued

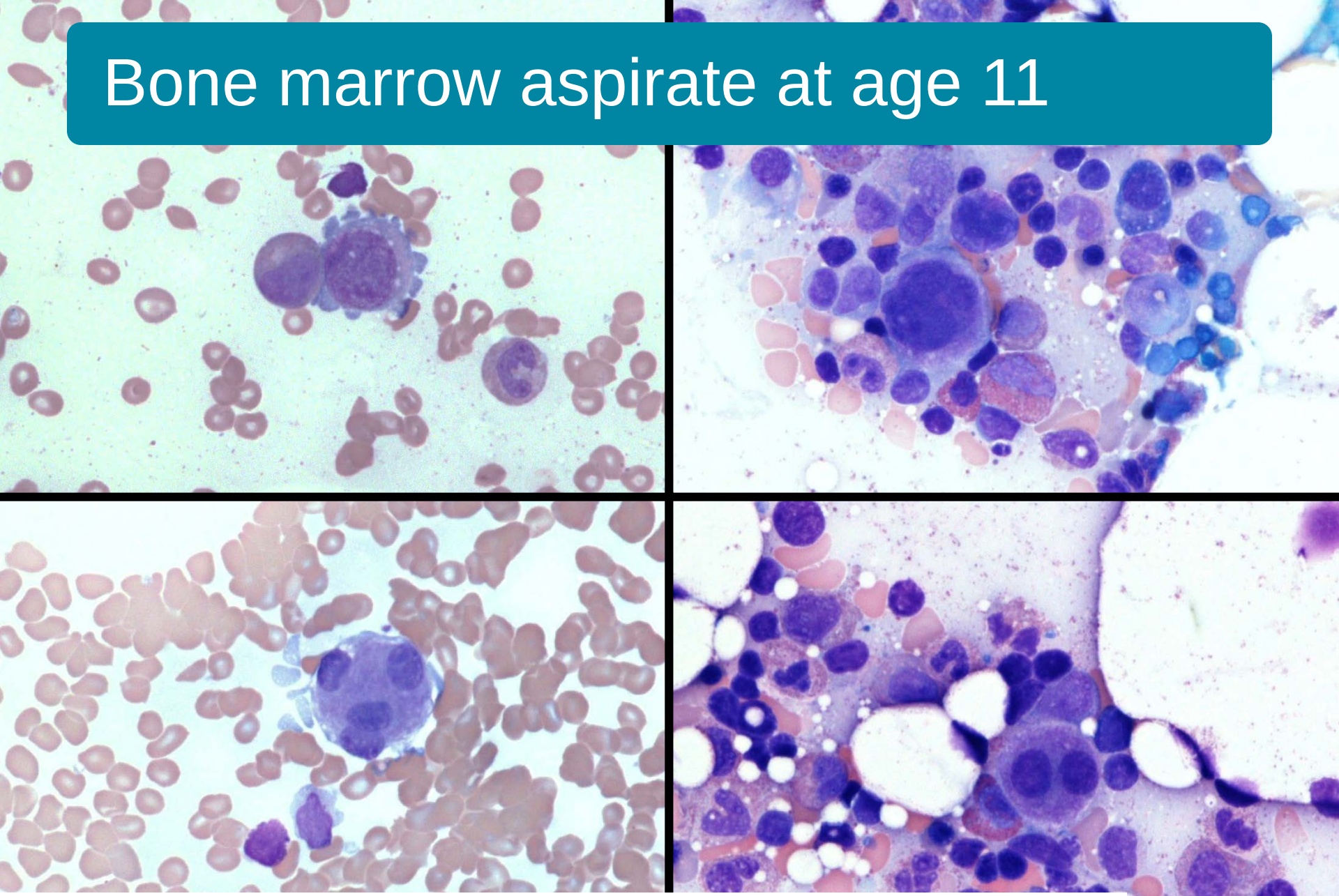
- Bone marrow aspirates and biopsies at ages 11 and 12
  - Mildly hypocellular marrow with megakaryocytic hypoplasia and dysplasia
  - Cytogenetics at age 11: 46,XY,?del(13)(q14q22)[2]/46,XY[18]
  - Cytogenetics at age 12: 46,XY,?del(13)(q14q21)[1]/46,XY[21]
  - FISH at both time points did not identify any abnormalities at 13q

Bone marrow aspirate at age 11



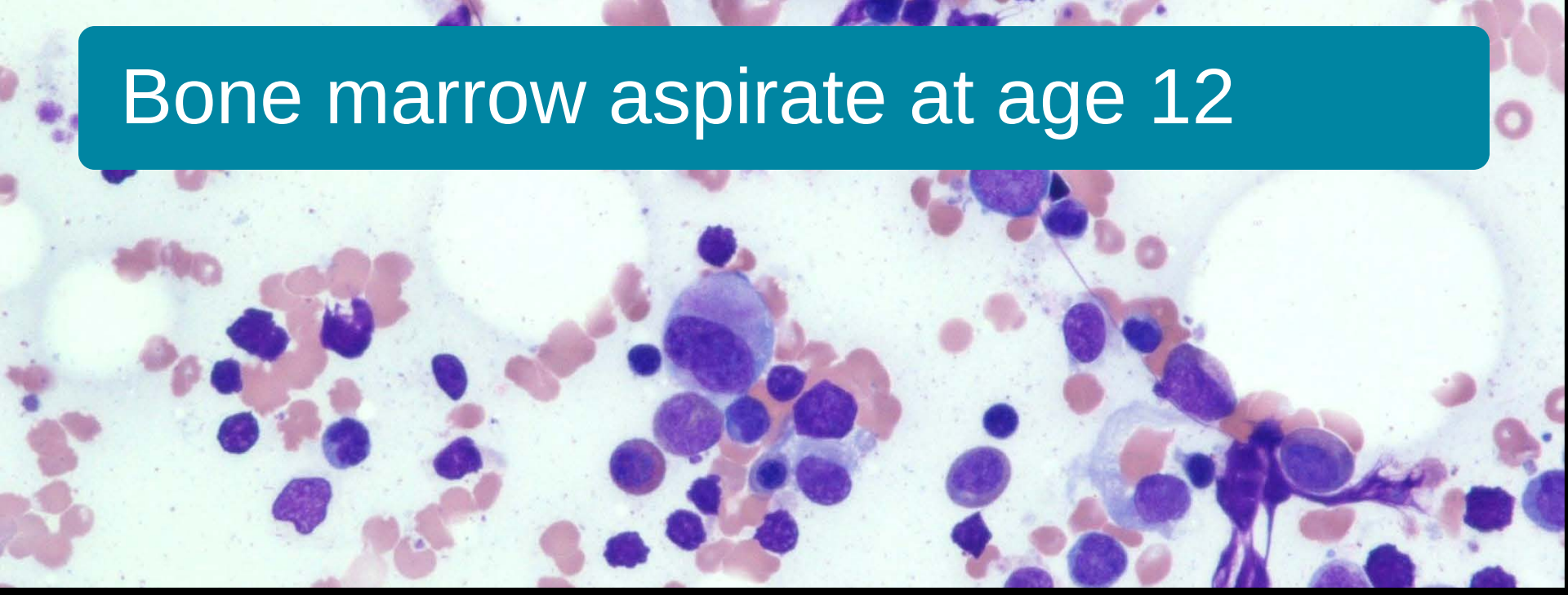
Small megakaryocytes with hypolobated nuclei

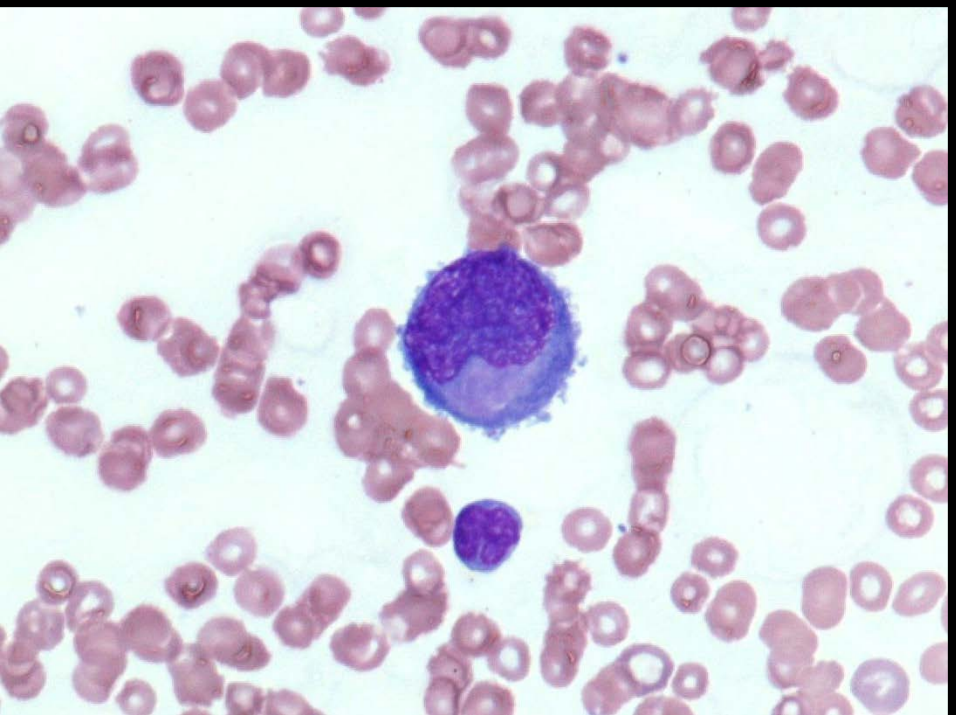
Bone marrow aspirate at age 11

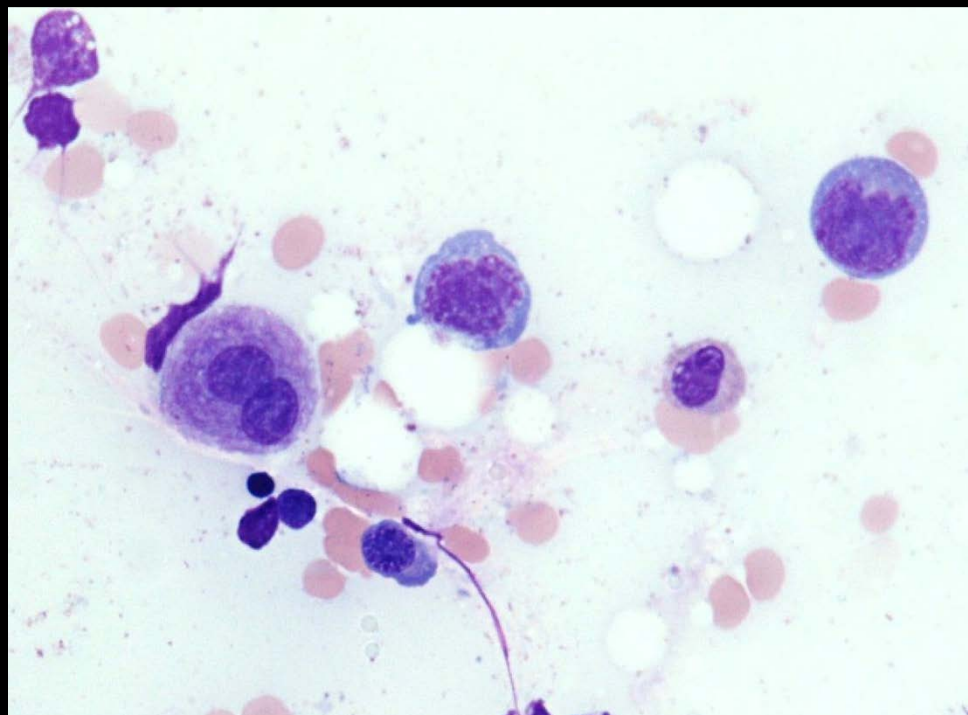


Small megakaryocytes with hypolobated nuclei, high nuclear-to-cytoplasmic ratios, and/or separate nuclear lobes

Bone marrow aspirate at age 12



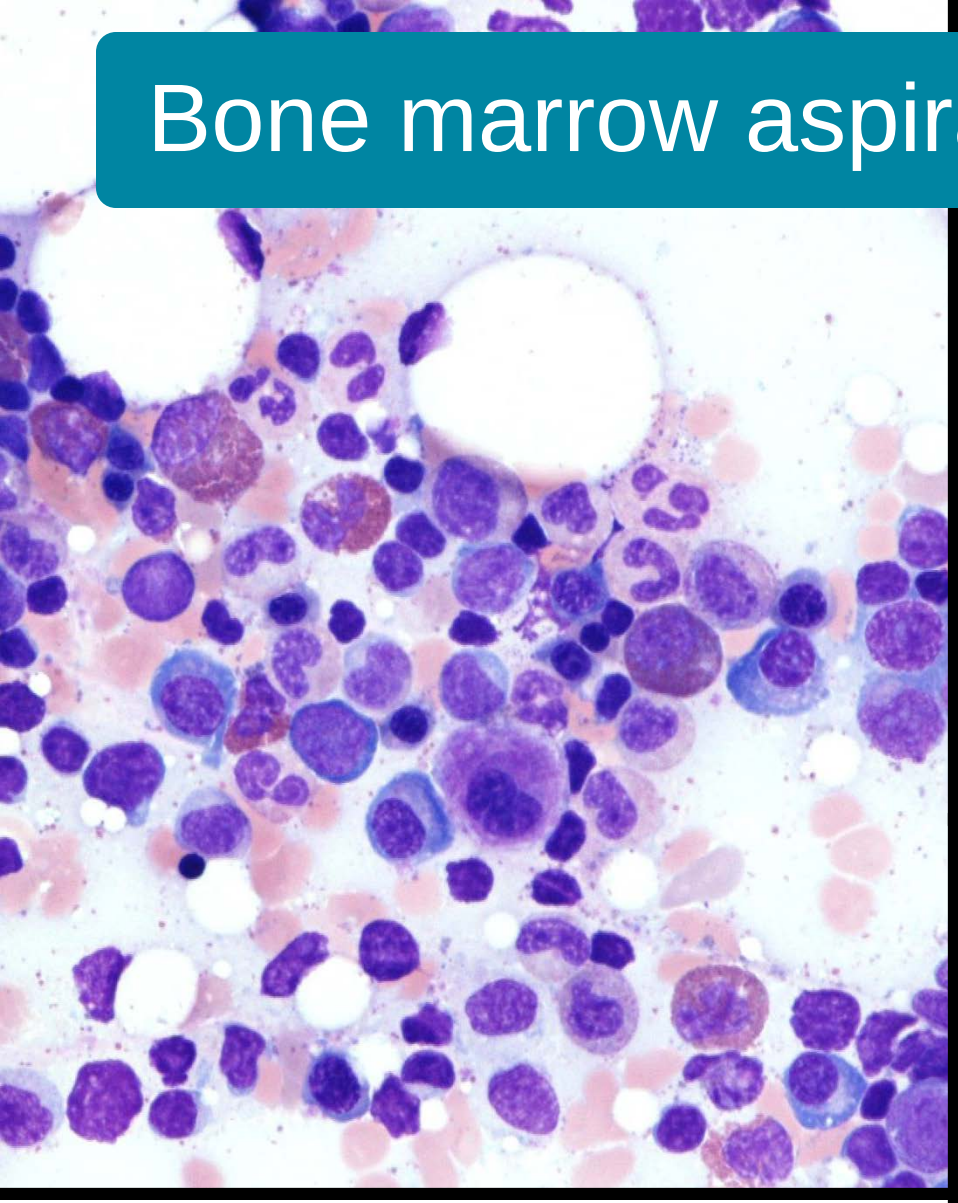


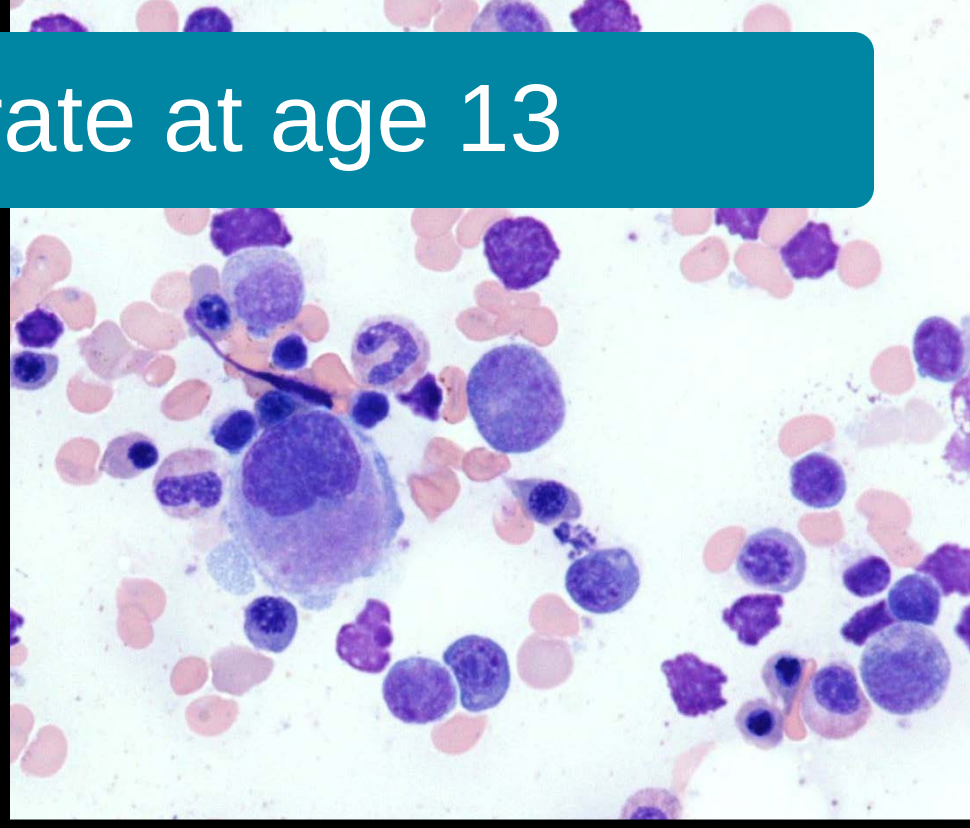


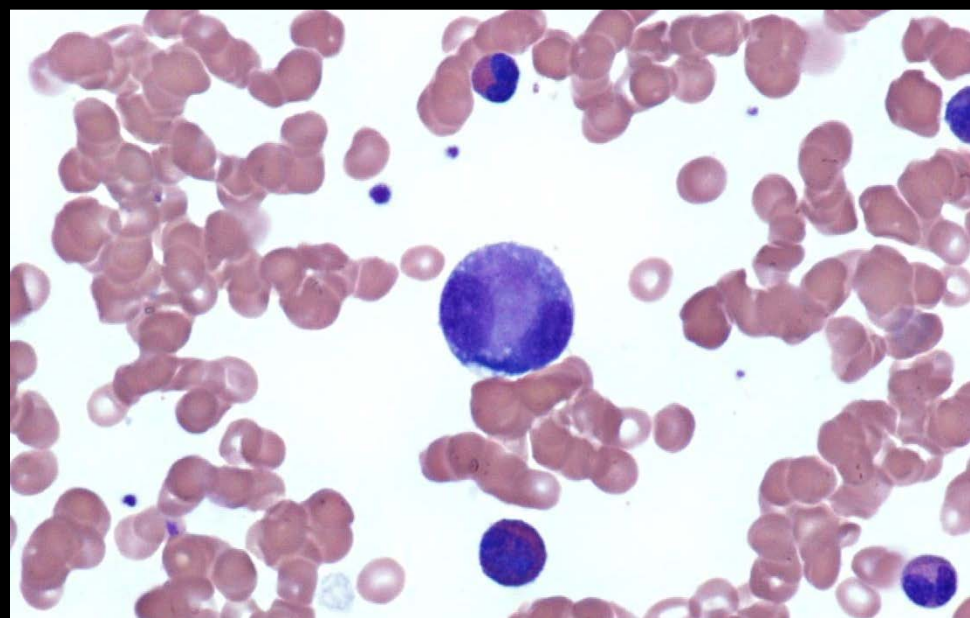
Clinical History, continued

- Presented at age 13 for annual routine bone marrow surveillance biopsy
- CBC
  - WBC 3.1 K/μL
    - ANC 899 /μL
  - Platelets 65 K/μL
  - Hemoglobin 12.4 g/dL

Bone marrow aspirate at age 13

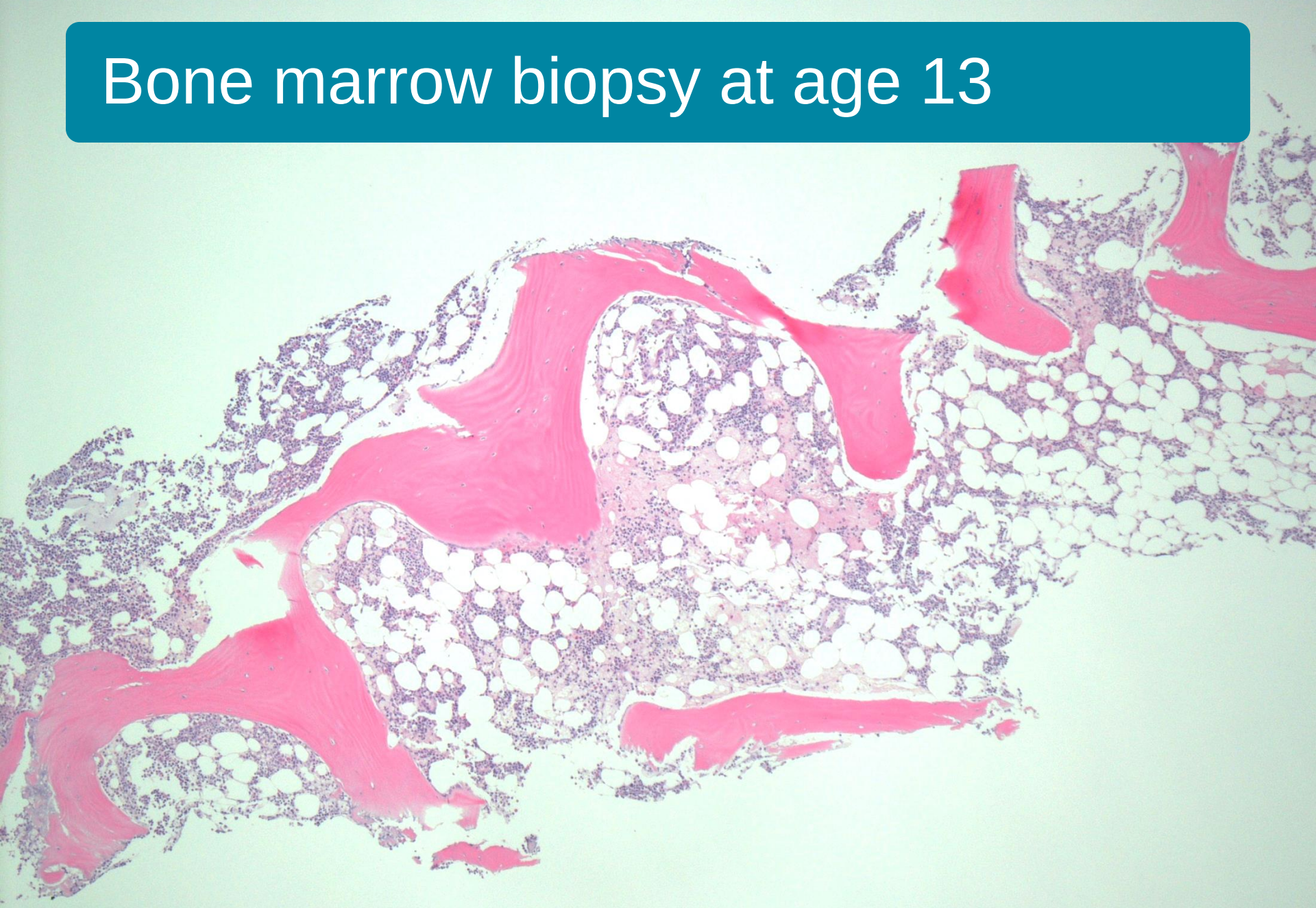






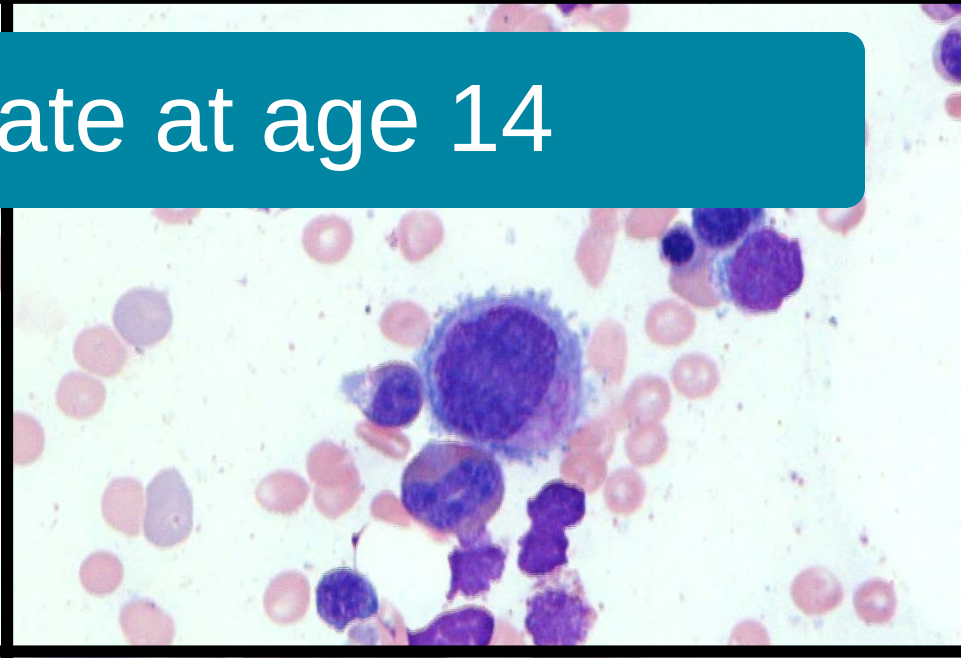
Smaller megakaryocytes with eccentric hypolobated nuclei and/or separate nuclear lobes

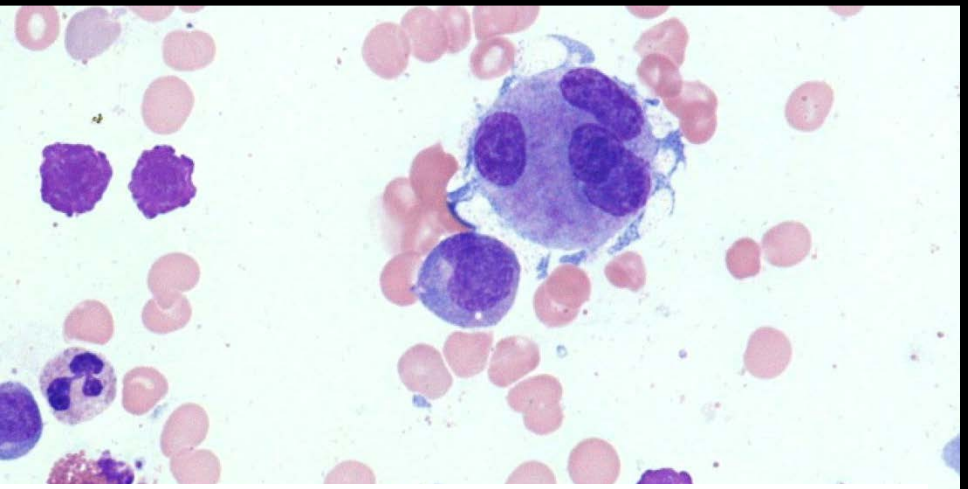
Bone marrow biopsy at age 13



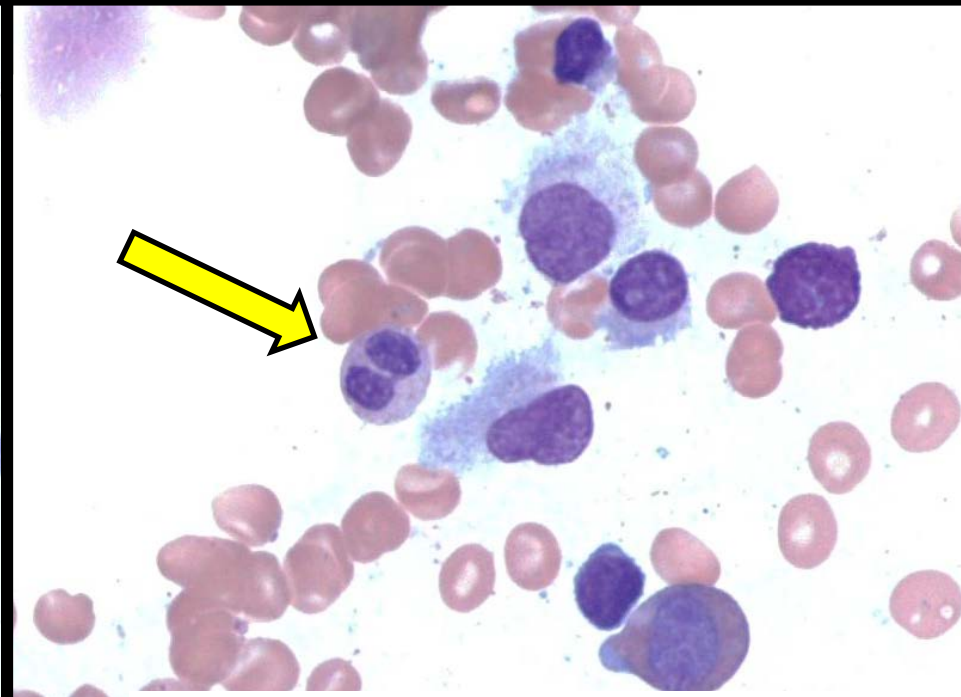
Normocellular to mildly hypocellular marrow

Bone marrow aspirate at age 14



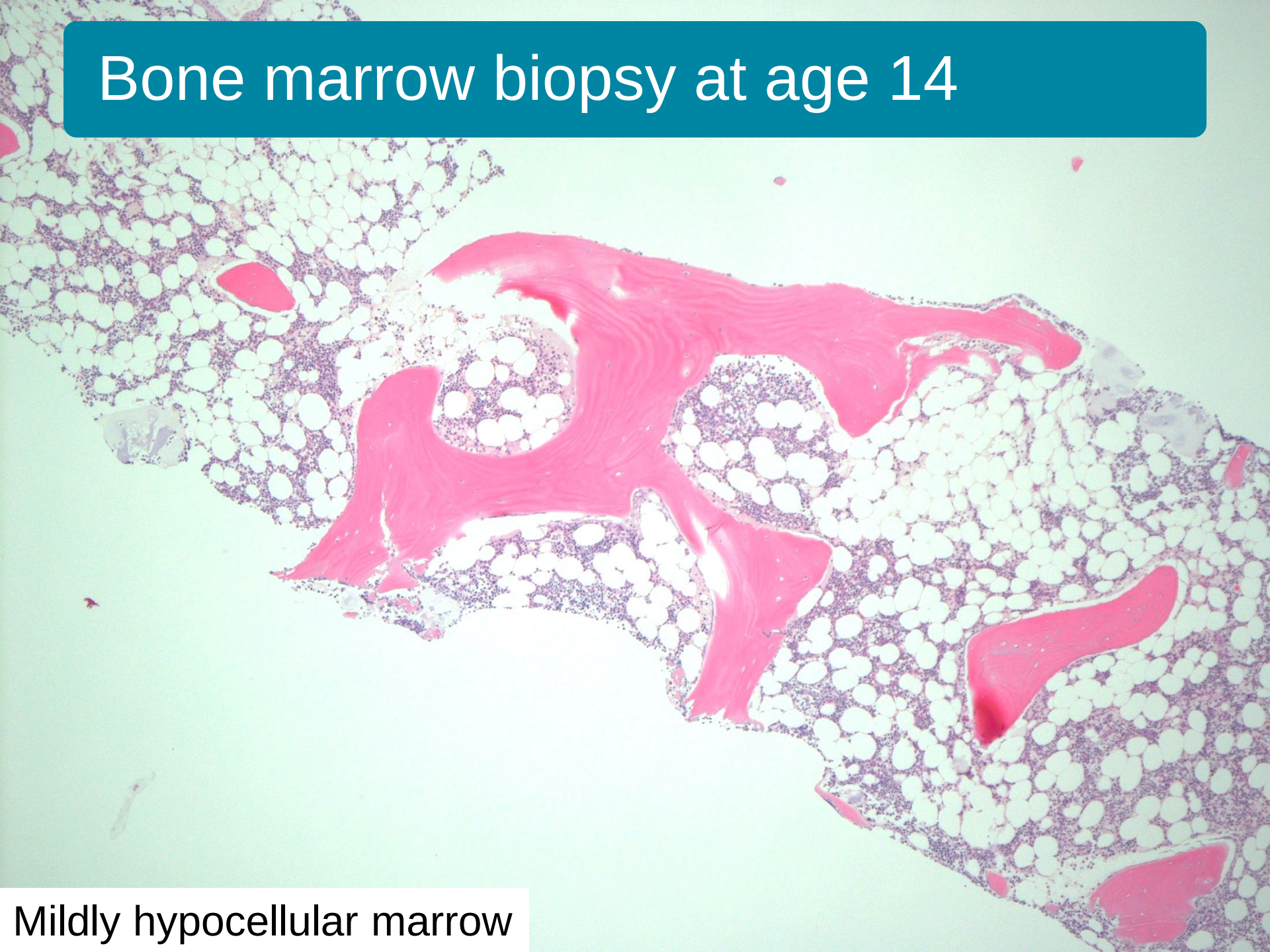


Smaller megakaryocytes with eccentric hypolobated nuclei, high nuclear-to-cytoplasmic ratios, and/or separate nuclear lobes



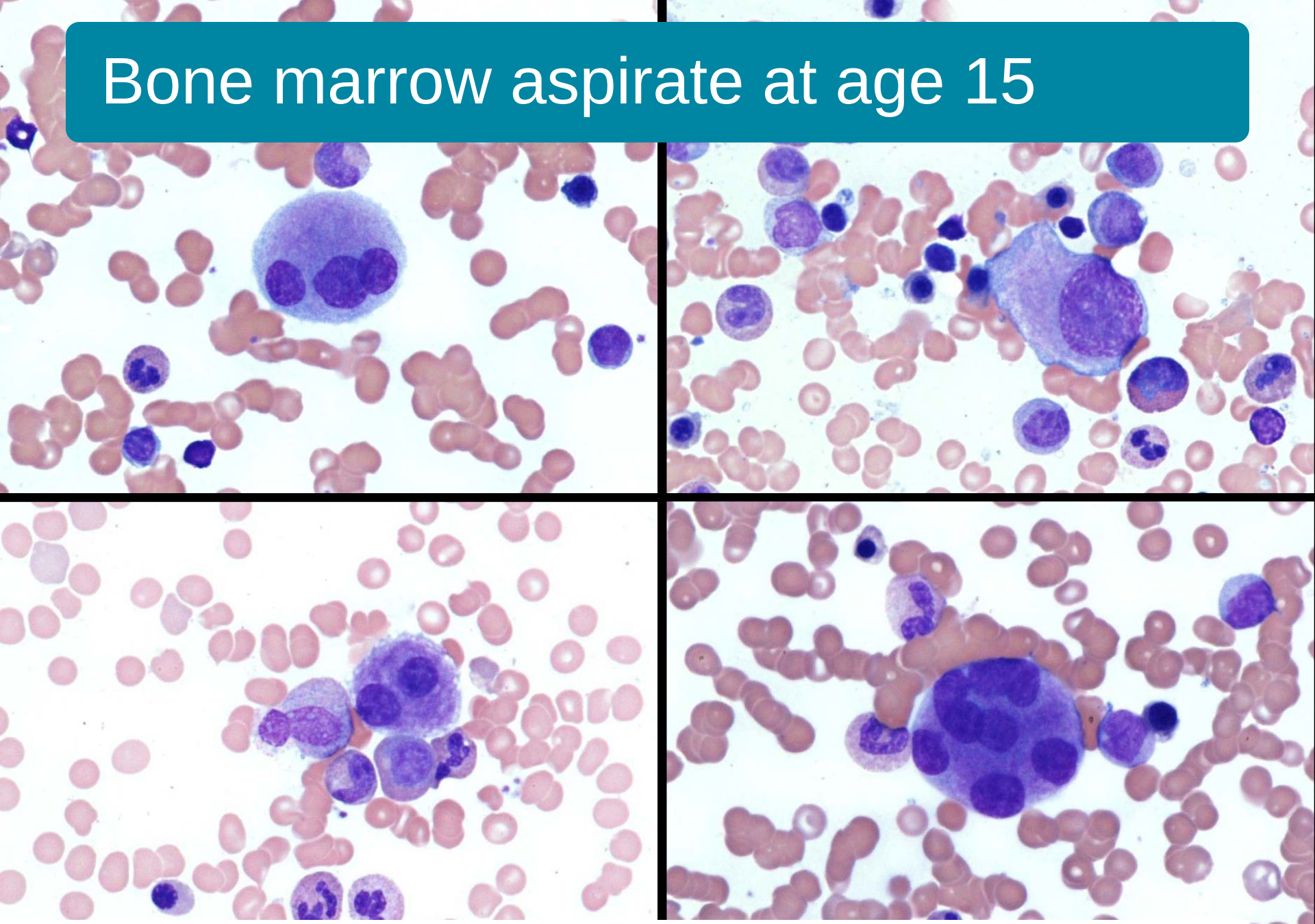
Pelger-Huet-like neutrophils

Bone marrow biopsy at age 14



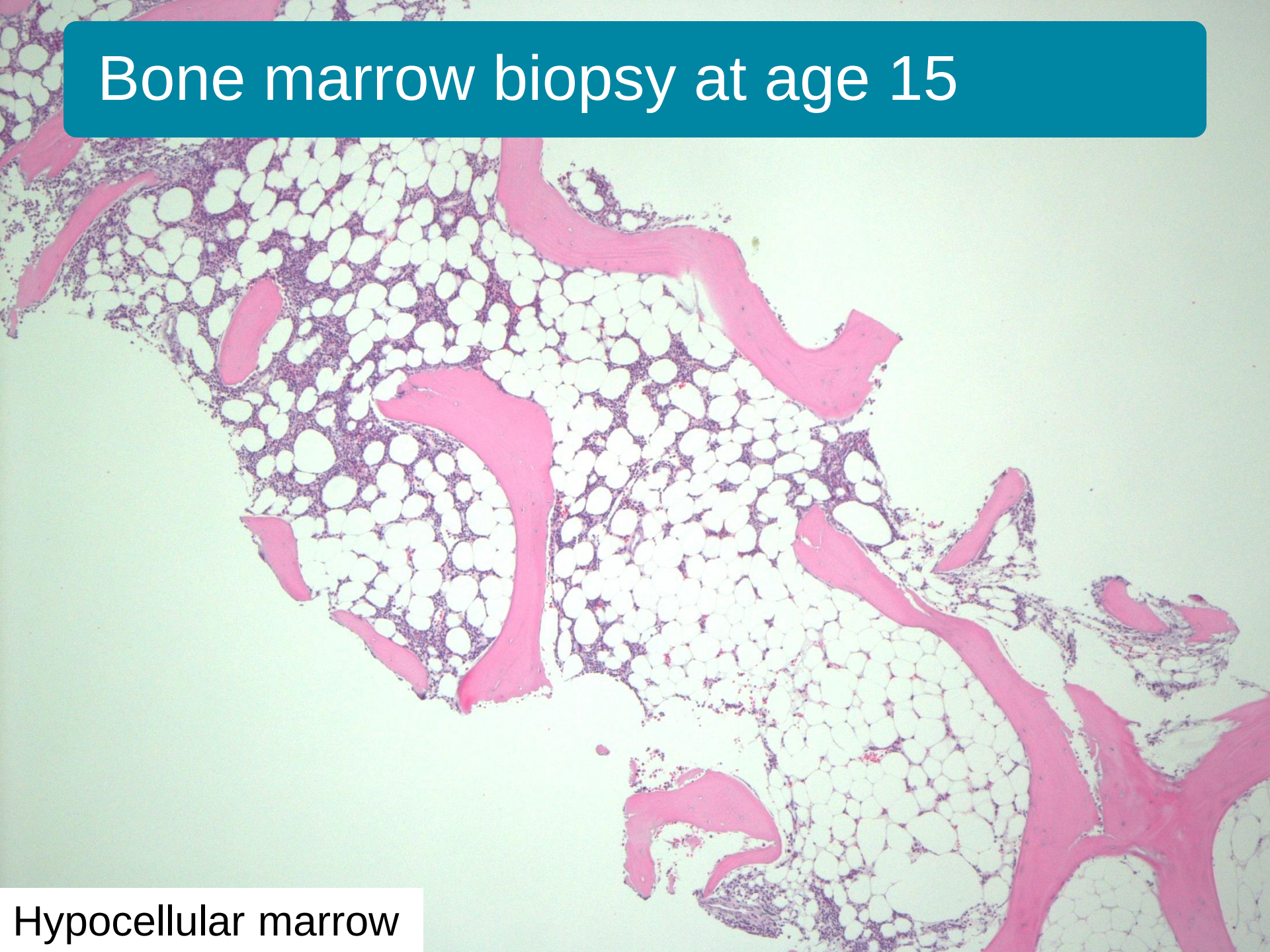
Mildly hypocellular marrow

Bone marrow aspirate at age 15



Megakaryocytes with separate nuclear lobes and/or small size

Bone marrow biopsy at age 15

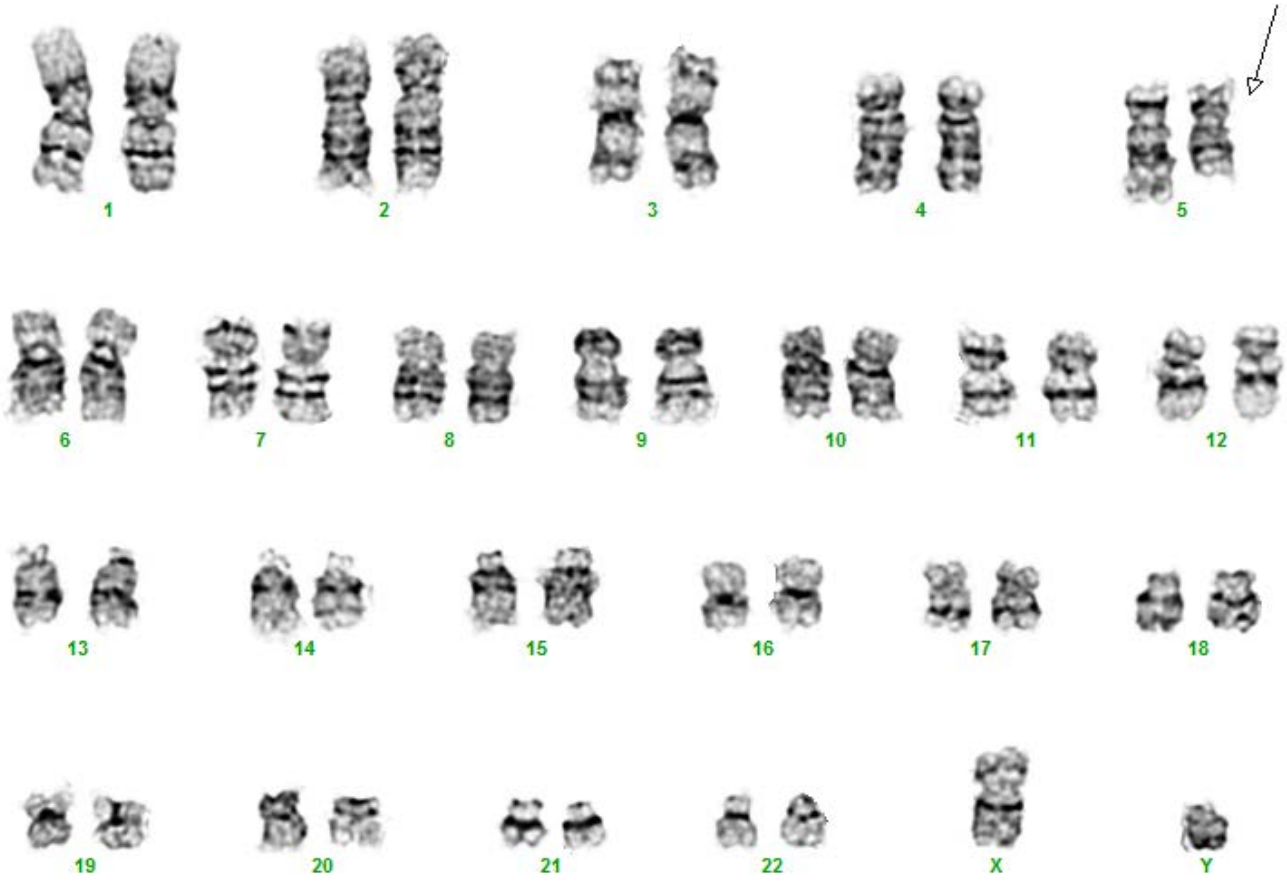


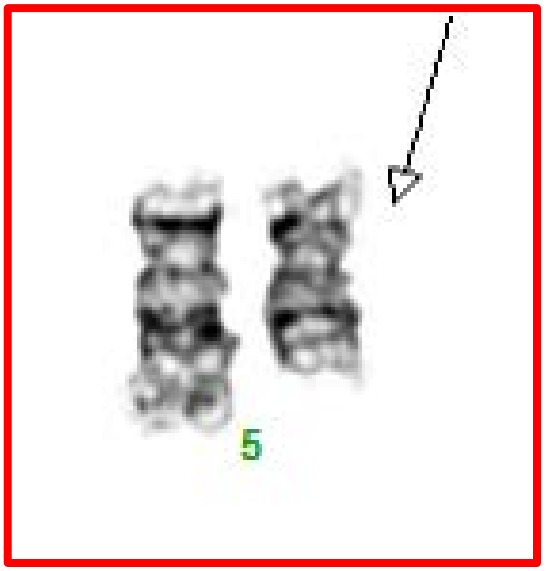
Hypocellular marrow

Flow cytometry at ages 13, 14, and 15

- No increase in blasts
- No abnormal populations

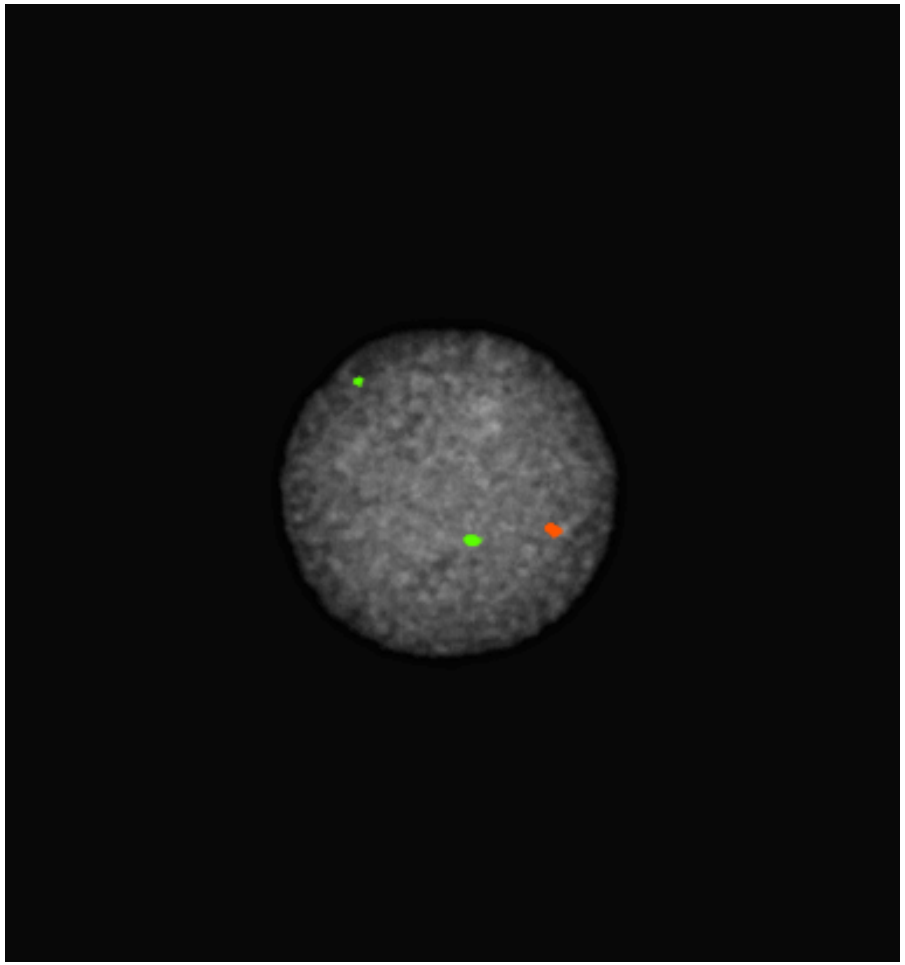
Cytogenetics at ages 13, 14, and 15





46,XY,del(5)(q21q3?1)[4]/46,XY[16]

FISH



Red = *EGR1* (5q31.2)

Green = D5630/D5S2064 (5p15.31)

Age 14 – del(5q) = 8%

Age 15 – del(5q) = 14%

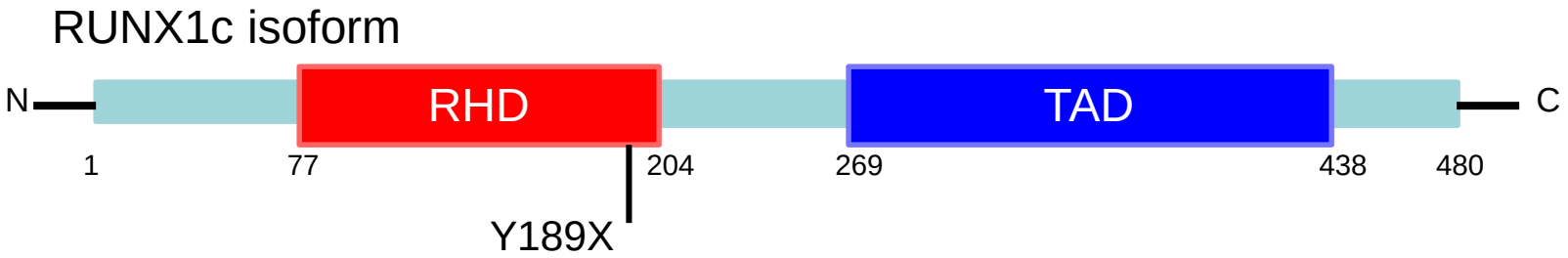
FISH negative for monosomy 7/del(7q), trisomy 8, del(20q)

Molecular findings

- Normal breakage studies of blood and fibroblasts to rule out Fanconi anemia
- Mildly abnormal telomere length analysis but not consistent with dyskeratosis congenita
- Normal Fragile X testing
- Normal comparative genomic hybridization (CGH) microarray
- No pathogenic *GATA2* mutations
- No *SBDS* mutations (Shwachman-Diamond)

Molecular findings

- *RUNX1* sequencing performed after the bone marrow at age 14
  - STOP mutation at Y189 (c.567C>G)



RHD = Runt Homology Domain - heterodimerizes with CBFβ to mediate DNA binding

TAD = transcriptional activation domain

Final Panel Diagnosis

Myelodysplastic syndrome with multilineage dysplasia with germline *RUNX1* mutation

Clinical Management

- Underwent mismatched unrelated double cord blood transplant 4 months after last bone marrow (3.5 months after the identification of the *RUNX1* mutation)
- Now 3 years from transplant and doing well

Thank you!

Final Panel Diagnosis:
Myelodysplastic syndrome with multilineage dysplasia with germline *RUNX1* mutation